Usage of Immunotherapy in Non-Small Cell Lung Cancer

Saathvik Reddy Pakhala

Introduction

Cancer, one of the most devastating diseases in history, occurs when cells uncontrollably divide instead of dying or stopping at checkpoints. These cells have the ability to bypass the immune system and damage healthy tissue, as well as spread to other areas of the body, therefore resulting in bodily harm or even death in some cases. The immune system is the body's way of defending itself against disease or infection by being able to fight off infection while recognizing its own cells. Ideally, the immune system has a set of mechanisms that should be able to defend against cancer, but the cancer cells mess with the immune system in order to bypass it and damage the body. To fight against cancer, the immune system should recognize the antigen and then send out T cells, Natural Killer (NK) cells, and antibodies from B cells in order to eliminate the threat for good. But, cancer cells can avoid this by either downregulating their MHC to identify them, or by overexpressing checkpoints like PD-1 or CTLA-4 to prevent activation of T-Cells. A potential solution to this problem though is immunotherapy. In immunotherapy, treatment is used to help boost the immune system in order to help it fight the disease more effectively. Because of this, immunotherapy can be seen as an attractive option to combat cancer as it can prevent the overstimulation of immune checkpoints. Plus, because of the methods immunotherapy uses, it can provide more effective, longer-lasting responses than conventional treatment methods. In this review, we will first describe the mutations and staging that are part of Non-Small Cell Lung Cancer (NSCLC), then examine how PD-1 and PD-L1 checkpoint inhibitors are able to prevent evasion of the immune system, analyze two current clinical trials covering neoadjuvant therapies and the optimal treatment duration, and ultimately consider newfound breakthroughs in the field utilizing biomarkers.

Main Body

Lung cancer can be divided into two different subcategories, Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). They differ because NSCLC has larger cells, as the name suggests, while SCLC is more aggressive, meaning it spreads more rapidly and can spread to other organs. Non-Small Cell Lung Cancer is an especially deadly and prevalent cancer variant, accounting for around 85% of all lung cancer cases (Basumallik & Agarwal, 2019) with no surefire cure. Luckily, advancements in the medical and scientific fields are surfacing new potential cures, one of which is immunotherapy. Immunotherapy is a treatment to attempt to modify or boost the body's immune system in order to use it to fight against cancer. NSCLC is primarily caused by heavy smoking or exposure to carcinogens, which damage the DNA of lung cells, prompting harmful, uncontrolled cell growth. NSCLC primarily affects adults over the age of 65, especially those who have a history of smoking tobacco (Lim et al. 2020). NSCLC also affects men more than women due to higher smoking rates, but East Asians are still more predisposed to NSCLC than other ethnicities (Zhou & Christiani, 2011). Furthermore, cultures and countries with higher smoking rates consequently have higher NSCLC rates, including China, Southeast Asia, Eastern Europe, and Russia. Some

common and underlying mutations in NSCLC include KRAS, EGFR, ALK and Tp53. KRAS is found in 25-30% of all NSCLC cases, but it is especially common in NSCLC cases in smokers (Al-Qaisi et al., 2025). KRAS is a point mutation in the gene that disturbs cell signaling pathways involved in regulating cell growth, causing uncontrolled growth (Al-Qaisi et al., 2025). EGFR (Epidermal Growth Factor Receptor) is prevalent in approximately 23% of cases, but it is even more common in non-smokers and Asian women who eventually contract adenocarcinoma (Al-Qaisi et al., 2025). The EGFR gene is supposed to produce proteins that help the cell grow and divide, but when mutated, it can create too much protein and cause excess cell growth and division. ALK (anaplastic lymphoma kinase) rearrangements are more mutations that are more common in younger non-smokers (Al-Qaisi et al., 2025). When fused with other genes it can cause cell proliferation and lead to uncontrolled, abnormal growth. Furthermore, patients with ALK positive or EGFR-mutated NSCLC shouldn't receive first-generation immunotherapy treatment since they are genomic-driven forms of lung cancer (Lim et al., 2020). This is due to the fact that these driver mutations are able to avoid the common ICI and TIL treatments, making immunotherapy less viable with a lower response rate. Instead, tyrosine kinase inhibitors (TKIs) work best for patients with these mutations, resulting in more effective care and significant increase in survival benefit (Lim et al., 2020). This is an important factor that can set ALK and EGFR mutations apart from the rest. Considering life expectancy, early-stage NSCLC is usually curable or treatable using the vast array of current treatments and technologies. On the other hand, individuals with later-stage NSCLC can have obtained irreversible damage and treatments can only potentially prolong their life by a few months or years. For example, individuals with Stage 1 (localized) NSCLC have a 5-year survival rate of 60-65%, while people with Stage 4 (metastatic) NSCLC have a 5-year survival rate below 10% (Al-Qaisi et al., 2025). Therefore there is no set life expectancy, since it depends on multiple factors including: stage, age/health, mutations, and the treatment options for those mutations. Treatment depends on the stage and aggressiveness of the cancer, allowing doctors to choose. During Stages 1 and 2, surgery can be combined with chemotherapy or radiation, to find a cure. During Stage 3, chemoradiation is combined with immunotherapy to attempt to find a cure or long-term control. Finally, in Stage 4, the most severe stage, targeted therapy and immunotherapy are used as final attempts to attempt to control the disease and prolong the patient's life.

In the vast majority of Non-small cell lung cancer (NSCLC) cases, NSCLC cells employ multiple immune evasion techniques, like manipulating the PD-1 and PD-L1 pathways, that make them more attractive targets for immune checkpoint inhibitors (ICIs). As seen in Das and Johnson's work, the role of these immune checkpoints is to ensure that deadly T cells do not get activated until a thorough verification with multiple steps. But, cancerous cells are able to use these checkpoints against the T cells by overexpressing them to turn off hordes of T cells, leaving the immune system with no response to fight the cancer (Das & Johnson, 2019). The most common kind of immunotherapy used against NSCLC is monoclonal antibodies used as immune checkpoint inhibitors. These monoclonal antibodies bind to the immune checkpoint of the T cell and prevent it from inhibiting T cell activation, allowing T cells to fight the cancer. The

three main proteins that get blocked in this type of immunotherapy are the PD-1 protein using drugs like nivolumab pembrolizumab, or cemiplimab, the PD-L1 protein using atezolizumab or durvalumab, and the CTLA-4 protein using ipilimumbab (Tang et al., 2022). While all of these ICIs target the T cells, combining these treatments with each other as well as chemotherapy is the most common route battling cancer (Tang et al., 2022). Some other treatments use targeted monoclonal antibodies, which are used to attack specific tumors with a certain antigen, but this usually works best with adenocarcinomas since they are more likely to have a tumor-specific antigen compared to squamous cell carcinoma (Al-Qaisi et al., 2025). Another form of immunotherapy used is T cell therapy, specifically tumor infiltrating lymphocyte (TIL) therapy. This form of immunotherapy requires the patient to have a few working T cells that aren't strong enough to fully eliminate the cancer on their own, and then involves isolating those cells and growing them in a lab before reinfusing them into the patient. By increasing the amount of T cells capable of fighting cancer and enhancing them in a laboratory, the immune system is able to create a stronger, more effective defense against cancer (Rosenberg & Restifo, 2015). While TILs show plenty of promise for the future, ICIs are still most commonly used along with chemotherapy due to their versatility, since the drug that is being used changes depending on what is overexpressed. Immunotherapy combined with chemotherapy can be effective at treating even advanced stage NSCLC cancer. For example, using just an ICI like pembrolizumab provided an objective response rate (ORR) of only 20% while using just chemotherapy provided an ORR of 29%. But when combining pembrolizumab with chemotherapy, the ORR jumped up to 55%, meaning it is very effective in the context of advanced NSCLC (Mok et al., 2019; Reck et al., 2016; Gandhi et al., 2018; Paz-Ares et al., 2018). Additionally, in the trial KEYNOTE - 189, pembrolizumab plus chemotherapy had a progression-free survival(PFS) rate of 8.8 months and a 12-month overall survival(OS) rate of 69.2%. When only chemotherapy was used, these numbers plummeted to a PFS of 4.9 months and an OS rate of 49.4% (Gandhi et al., 2018). As seen in this trial, the effectiveness of treatment is heightened when chemotherapy and immunotherapy like ICIs are combined. In lower stage NSCLC, just immunotherapy, chemotherapy, or surgery work fine on their own, and ICIs are extremely effective and in lower stages. Like all cancer treatments, there are limitations to these ICIs that come along with its advantages. ICIs can be pretty ineffective as a monotherapy as seen in the data above, and they also need antigen-specific T cells—cells that express PD-L1 as a biomarker— to be present so doctors can know what to target and what to use. Some patients don't have the tumor cells which express PD-L1 enough, leaving the ICI without a target to attack (Mok et al., 2019). Patients can also resist treatment, and the resistance is categorized into primary and acquired resistance. Primary resistance occurs when the patient's cells don't respond to the treatment from the start, meaning the ICIs never had a benefit (Lim et al., 2020). Alternatively, acquired resistance occurs when patients initially respond to treatment with a short period of beneficial growth, but experience further disease progression midway through the treatment (Tang et al., 2022). All of these resistance mechanisms need to be accounted for and worked around in order to make ICIs an effective

treatment, adding to the challenge. Furthermore, since ICIs activate hordes of T cells in an attempt to fight the cancer, the T cells can attack themselves and cause autoimmune disorders which would hurt the patient instead of help. In fact, around 70-90% of patients using ICIs experience some sort of an immune-related adverse effect (irAE), but only 10-30% of patients experience severe (grade 3-4) irAEs (Das & Johnson, 2019). These numbers do vary though depending on the ICI the patient is treated with the and the severity of their cancer. All of these ICI immunotherapies are FDA approved and currently being used to help save the lives of multiple patients. Pembrolizumab, the main ICI used in these combination therapies, gained FDA approval for the first-line treatment of PD-L1 positive metastatic NSCLC in 2016. Beyond that, pembrolizumab has a PD-L1 threshold requirement of 50% or higher, which is frequently taken into consideration during treatment. Nivolumab, a common secondary option, was given approval for second-line treatment in 2015 (Tang et al., 2022; Lim et al. 2020).

In the scientific field, over 1,500 clinical trials are investigating NSCLC immunotherapy in order to maximize the effectiveness and usage of immunotherapy. One study, focusing on neoadjuvant Immunochemotherapy vs chemotherapy (further referred to as Study 1) is attempting to compare the effectiveness of neoadjuvant chemotherapy to neoadjuvant immunochemotherapy. Neoadjuvant treatments are administered in smaller doses prior to the main treatment, surgery, in order to shrink the tumor and make the surgery easier. Specifically, this study wants to learn more about neoadjuvant immunochemotherapy and its patterns, efficacy, real-world usage, and prognosis. The NCT number of this study is NCT05974007. The other study is on PD1/PDL1 inhibitors, a specific type of immunotherapy, and their ideal treatment duration in patients (Referred to as Study 2). In this study, one group of patients uses these inhibitors, specifically Atezolizumab, Nivolumab, and Pembrolizumab, for 24 months while the other cohort uses it past 24 months by clinical choice. First of all, let's go through a quick overview of these drugs. All 3 of them focus on the PD-1/PD-L1 immune checkpoint pathway, not the CTLA-4 pathway. Pembrolizumab mainly targets the CD8+ T cells, restoring their tumor cell killing functions, but also has the CD4+ T Cells as a secondary target. Nivolumab is very similar to Pembrolizumab, restoring the cytotoxic ability of CD8+ T cells and blocking PD-1 on both CD8+ and CD4+ T cells. Atezolizumab is different from the other ones because it is actually expressed on the PD-L1 pathway instead. And while it still affects both CD8+ and CD4+ T cells, the primary function is to prevent tumor cells from turning off these T cells, not making them stronger. The primary focus is to find the ideal duration of immunotherapy treatment to minimize negative side and long-term effects while maximizing effectiveness. But this study has secondary focuses as well, including assessing the outcomes post-disease progression in patients who stopped treatment after 24 months, and identifying biomarkers to help scientists predict long-term outcomes and responses. As seen in the plans, both studies have a cohort-based observational model, but what sets Study 1 apart is that it has a retrospective time perspective, while Study 2 is a miscellaneous mix. Both studies are currently recruiting participants to evaluate their respective treatment approaches. Also, both studies have the same indication, to find the most efficient method and drugs to reach a cure for NSCLC. Like all

studies, both Study 1 and Study 2 have inclusion and exclusion criteria, which determine which patients are allowed to volunteer. For Study 1, patients entering must have a Stage I-III NSCLC diagnosis, and must have no history of malignant tumors or any current ones, without any anti-tumor treatment. Furthermore, patients must have at least 1 measurable lesion, have organs able to tolerate surgery, and be between 18-85 years old. Finally, patients must have previously gone through neoadjuvant ICIs and/or chemotherapy, and then go through radical surgery. The 2 exclusion criteria this study has are that the study excludes patients included in anti-tumor drug intervention or unblinded clinical trials where the administered treatment is unknown. As well as excluding patients who have had prior surgery, radiotherapy, or systemic therapy for NSCLC. For Study 2, patients must have a NSCLC diagnosis, be over 18 years old, go through at least 24 months of treatment with one of the three ICIs with at least 3 months of follow-up or death after stopping. Furthermore, the patient must have consented, have their illness measurable by Response Evaluation Criteria in Solid Tumours (iRECIST) criteria, and have a complete response, partial response, or stable response at the end of the treatment, in the absence of disease progression. Patients excluded from this study are those who have been through chemo-immunotherapy previously or are associated with other immunotherapy or other drugs in clinical trials. Also, patients who permanently discontinue treatment for many reasons, patients who have had more than three loco-regional treatments to maintain the radiological response, and patients who have had a suspension of immunotherapy for longer than 40 days during the 24 month treatment are excluded from the study. Both studies don't have any specific performance-status scores required for their patients, they just go off of a set of criteria a patient must follow. Another similarity that both treatments have is that they both study T-cells, and how cancer cells are able to bypass the immune system by overexpressing their immune checkpoints. Both treatments involve immune checkpoint inhibitors, to combat the overexpression of immune checkpoints, but Study 2 is more specifically focused on PD1/PDL1 inhibitors. Study 1 addresses the previous limitations that higher stage NSCLC can be too extensive for surgery to take care of on its own and that too much immunochemotherapy can have negative effects. Study 1 does this by limiting the usage of immunochemotherapy and radiation and using immunochemotherapy to shrink the tumor to a small enough size for surgery to remove. Study 2 addresses the problem that there isn't enough data to determine how long the ideal treatment duration for immunotherapy ICIs is, and attempts to get rid of negative side effects. The study attempts to do this by trying to find a sweet spot so that the patient gets effective help, while not having to face many negative side effects, so they try multiple durations to find the right one. In general, the future of immunotherapy in NSCLC is looking extremely positive. Scientists are starting to move beyond common PD-1/PD-L1 monotherapy and are now using them in novel combination therapies in order to enhance the treatment's effectiveness. Examples of these combo-therapies include combining ICIs with chemotherapy, or using multiple ICIs like combining PD-1 and CTLA-4 inhibitors to target multiple pathways at once, lowering dosage and exposure (Tang et al., 2022). The only potential issue with this is that increasing the number of checkpoint inhibitors can increase the risk of severe irAEs in patients

(Tang et al., 2022). Sometimes though, only targeting checkpoint pathways can be inefficient and ineffective, that's where biomarkers come in. As of right now, PD-L1 expression is used as a biomarker, but the future is trending towards multi-parameter biomarkers that factor in tumor mutational burden, expression profiles, and immune cell infiltration to achieve more precise patient treatment selection. (Tang et al., 2022). Another popular treatment is tumor-specific neoantigens, which uses the specific neoantigen each tumor uses to target a specific type of cell. While it is still early in development, neoantigen immunotherapy has the ability to be extremely personalized and effective, but could be challenged by tumor heterogeneity and is difficult to mass produce (Lim et al., 2020). While all of these encouraging avenues are possible, many of them are still just drafts and haven't gone through proper testing yet to become widespread. Nonetheless, the future for NSCLC immunotherapy is getting brighter day by day.

Conclusion

This paper covered the usage of immunotherapy in NSCLC, which is a common type of lung cancer in which larger cells grow out of control in the lungs. NSCLC is treated well by immunotherapy, but is much more effective when combined with other treatments like chemotherapy. This is because it directly targets the methods that NSCLC uses to avoid the immune system by blocking the immune checkpoints, making it really successful. Due to the most common mechanism of evasion being through these immune checkpoints, the most impactful type of immunotherapy has been in the form of ICIs. When used with chemotherapy, ICIs have been shown to have over a 55% objective response rate, making it very effective in this realm. Professionals in the field are currently working on achieving all of the benefits of immunotherapy without the risks. Due to the immense activation of T cells that result from ICIs, immunotherapy can cause autoimmune disorders where the body attacks itself, actually worsening the patient's condition instead of helping. Looking ahead, immunotherapy can change the field of cancer treatment forever, with further research on the combinations of therapies rapidly boosting development. Immunotherapy could potentially become the new way to treat cancer for good.

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